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Title page

A single-arm, non-randomized and open-label phase 3 study evaluating the efficacy, safety and tolerability of intravitreal aflibercept in Japanese patients with neovascular glaucoma (NVG)

Japanese phase 3 study of aflibercept in NVG patients [VENERA]

Bayer study drug	BAY86-5321/Aflibercept/Eylea		
Study purpose:	Efficacy and Safety		
Clinical study phase:	III	**Date:**	7 Sep 2018
Study No.:	19652	**Version:**	1.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CRVO	Central retinal vein occlusion
FAS	Full Analysis Set
IOP	Intraocular pressure
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
NVA	Neovascularization of the angle
NVG	Neovascular glaucoma
NVI	Neovascularization of the iris
OIS	Ocular ischemic syndrome
PDR	Proliferative diabetic retinopathy
PPS	Per Protocol Set
PRP	Photocoagulation
PT	Preferred Term
SAF	Safety Analysis Set
SOC	System Organ Class
VEGF	Vascular endothelial growth factor
WHO-DD	World Health Organization Drug Dictionary
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CRVO	Central retinal vein occlusion
FAS	Full Analysis Set
IOP	Intraocular pressure
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
NVA	Neovascularization of the angle

1. Introduction

Treatment of Neovascular Glaucoma

The clinical manifestations of NVG include elevated intraocular pressure (IOP) and neovascularization in the anterior segment of the eye (iris and/or anterior chamber angle). Therefore, a combined approach is used to both reduce IOP and promote regression of neovessels. Panretinal photocoagulation (PRP) is commonly used to treat ischemic retina, induce regression of neovascularization in the anterior segment, and reduce IOP. The effects of PRP are not produced immediately, and during this period, further neovascularization may be seen and the anterior chamber angle may become progressively occluded worsening the prognosis. Moreover, it is often difficult to perform PRP in eyes with NVG, due to corneal edema secondary to high IOP or to other opacities of the optic media such as cataract or vitreous hemorrhage. If PRP is suboptimal, cryo-coagulation is conducted or endolaser coagulation may be combined with vitreous surgery. Despite such invasive treatments, progression of the neovascularization may continue because of persistent ischemia. The role of intravitreal anti-VEGF is to produce a fast regression of the anterior segment neovascularization, stabilizing disease progression and bridging the patient to a long-term solution after the effect of PRP is attained.

About BAY 86-5321 (aflibercept)

The recombinant protein aflibercept exhibits very potent binding activity to human VEGF, with an equilibrium dissociation constant (Kd) of approximately 0.5 pM. This binding activity is more potent relative to the activity of anti-VEGF agent ranibizumab (with a Kd in the order of 100 pM). The formulation, aflibercept, is developed for intraocular use. Research using an animal ophthalmological disease model demonstrated that aflibercept adequately inhibits the incidence of retinal neovascularization, choroidal neovascularization (CNV), and retinal edema.

Intravitreal administered anti VEGF drugs may be able to halt this process and even regress neovascularization by directly inhibiting VEGF. Therefore, anti VEGF drugs, Aflibercept, shall be recommended for testing the efficacy in patients with NVG. Given the well established safety profile of aflibercept in various indications and the reports of anti VEGF therapies successfully given to patients with NVG, the applicant plans an additional study, No. 19652, with the mean change in IOP as the primary endpoint for the purpose of evaluating IOP lowering effect and at the same time neovascularization of the iris (NVI) regressing effect as the secondary endpoint.

This statistical analysis plan (SAP) is based on the following protocol:

- Clinical Study Protocol, Version 1.0, dated 18 May 2018

2. Study Objectives

Primary objective:

- To assess the efficacy of intravitreal (IVT) administration of aflibercept on the change in IOP in patients with NVG.

Secondary objective:

- To assess the safety and tolerability of IVT administration of aflibercept in patients with NVG.

3. Study Design

Design overview

This study will enroll NVG patients. This is a multicenter, single-arm, non-randomized, and open-label phase 3 trial to evaluate the primary efficacy variable "change in IOP from baseline to Week 1" of IVT administration of aflibercept in NVG patients (Figure 3-1).

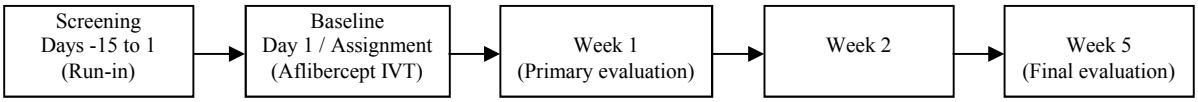

Figure 3-1 Study outline

After eligibility is confirmed, subjects will initiate treatment with at least 3 of the 5 allowed classes of topical IOP-lowering drugs. With application of the first eyedrop, the run-in-phase will start and IOP is monitored to determine whether the subject qualifies for assignment. If IOP is higher than 25 mmHg and all other criteria allow, the subject should be assigned and given aflibercept. Treatment with topical drug classes initiated during Run-in phase should be continued unchanged until Week 1.

If required, subjects can receive systemic IOP-lowering drugs, or undergo PRP or surgery intended to lower IOP, during study participation. Even if medically justifiable, any of these IOP-lowering interventions should not be performed before the primary endpoint visit. If IOP-lowering intervention is unavoidable or systemic IOP-lowering drugs are needed for the treatment of the study eye and/or fellow eye before the primary-endpoint visit, the evaluations of the Week-1 visit should be done before the intervention.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data. Graphical displays may also be used to summarize the data.

Applicable standards are as follows:

- Global Standards for Data Displays Version 3.0, dated 16 Jan 2017,
- Global Standard Tables Version 3.0, dated 16 Jan 2017, and
- Global Standard Listings Version 3.1, dated 16 Jan 2017.

The statistical analysis plan can be updated based on the result of the validity review meeting before database lock.

A detailed overview of the tables, figures, and listings that will be created can be found in the corresponding Table, Listing, and Figure (TLF) Specification document.

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been assigned. Subjects who are withdrawn from the study after assignment, or who prematurely discontinue the study will not be replaced.

The number of subjects who discontinue prematurely (i.e., screening failure and dropout, respectively) will be summarized by reason for premature discontinuation.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

In principle, last observation carried forward (LOCF) will be used to impute missing data for efficacy analysis. Baseline values will not be carried forward, but unscheduled assessments after baseline will be utilized if available. The further detail is described in Sec 6.2 Efficacy.

Efficacy Variables

If no valid IOP is available at the Week 1, the last post baseline before Week 1 will be utilized for imputation. If the prohibited treatment will be received, the IOP after prohibited treatment will not be utilized for imputation in PPS analysis. On the other hand, the IOP after prohibited treatment will be utilized in FAS analysis. The same imputation rule will be conducted for NVI and Neovascularization of the angle (NVA).

Safety Variables

No imputation for safety analyses is planned.

4.4 Interim Analyses and Data Monitoring

No formal interim analysis is planned.

4.5 Data Rules

Baseline value

In principal, baseline values are defined as the latest valid pre injection assessments.

Unscheduled assessments

Unless otherwise specified, extra assessments (e.g. vital signs associated with non protocol clinical visits or obtained in the course of investigating or managing adverse events[AEs]) will be included in data listings, but not in data summaries. If more than one measurement is available for a given visit, the first observation will be used in the data summaries and all observations will be presented in the data listings.

Coding

Medical history findings and AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and medications including surgery by Anatomical Therapeutic Chemical (ATC) codes (World Health Organization Drug Dictionary [WHO-DD]).

4.6 Blind Review

The results of the final data assessment will be documented in the final list of important deviations, validity findings, and assignment to analysis set(s). Any changes to the statistical analyses prompted by the results of the review of study data will be documented in an amendment and any change after the final validity review meeting will be documented in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.6).

Full Analysis Set (FAS)

The FAS will include all subjects who;

- are assigned,
- received at least one IVT administration of study drug on Day 1,
- have baseline valid IOP measurement, and
- have at least one post-baseline IOP measurement before or at Week 1.

The FAS will be used for supplemental analyses in efficacy.

Per Protocol Set (PPS)

The PPS will include the all subjects who;

- are assigned,
- received at least one IVT administration of study drug on Day 1,
- have baseline valid IOP measurement,
- have at least one valid (e.g., measured during valid time window and before prohibit treatment) post-baseline IOP measurement before or at Week 1, and
- show no validity findings that may affect efficacy.

  e.g., meet all of inclusion criteria, do not meet any exlusion critriea

The efficacy variables, which measured within four days from the dose (the day included), will be excluded from analyses in PPS because the effect occurring of drug may assumed to need a few days according to mechanism of action of aflibercept. The post baseline IOP, which measured two hours before or after the measurement clock time at baseline, will be excluded from analyses in PPS in order to exclude diurnal variation of IOP[1]. The PPS will be the primary analysis set for efficacy analyses.

Safety Analysis Set (SAF)

The SAF will include all subjects who are assigned and received at least one IVT administration of study drug.

6. Statistical Methodology

6.1 Population characteristics

6.1.1 Subject validity and disposition

Study sample size and subject validity reasons for exclusion from analysis will be summarized using frequency tables. Subject disposition: end of treatment i.e., Week 1 and end of follow-up i.e., Week 5 will be summarized.

6.1.2 Demography

Demographic and other baseline characteristics will be summarized for the SAF. If the other analysis sets (i.e., FAS, and PPS) differs from the SAF, the same analyses will be also conducted in the each analysis set.

Demography includes:

- Age (years),
- Sex,
- Ethnicity,
- Race,
- Body height (cm),
- Body weight (kg),
- Body mass index (kg/m^2),
- Vital signs (temperature, blood pressure, and pulse), and
- Smoking history.

Baseline characteristics include:

- Primary underlying disease leading to development of NVG,
- Stage of NVG,
- Duration of disease (days),

  Duration of disease = first study drug administration date - NVG diagnosis start date
- IOP (mmHg),
- NVI grade, and
- NVA grade.

6.1.3 Medical history

These analyses will be conducted in the SAF. If the other analysis sets (i.e., FAS, and PPS) differs from the SAF, the same analyses will be also conducted in the each analysis set.

Medical history findings will be summarized using frequency tables presented by MedDRA term. This summary will be also provided for ocular (study eye and fellow eye, respectively) and non-ocular findings.

6.1.4 Prior and concomitant therapy

Medications

These analyses will be conducted in the SAF. If the other analysis sets (i.e., FAS, and PPS) differs from the SAF, the same analyses will be also conducted in the each analysis set.

The number of subjects who took the following medication will be summarized using frequency tables presented by WHO-DD ATC subclass within ATC class.

- medications that started and ended before the start of study drug

- medications that are ongoing at or began after the start of study drug
- medications that are ongoing at the start of study drug
- medications that began after the start of study drug

The number of subjects who took systemic IOP-lowering drugs will be also summarized.

6.1.5 Study Drug Exposure

These analyses will be conducted in the SAF.

Total number of study drug administered during the study period will be summarized using frequency tables.

6.2 Efficacy

The PPS is the primary analysis set for efficacy. The FAS is a set for supplemental analysis of the PPS analysis. No alpha adjustment for multiple comparisons was considered, because confidence interval of other analyses except the primary analysis in PPS will be interpreted in consideration of false positives due to multiple testing.

6.2.1 Primary efficacy analysis

Primary efficacy variable is

- Change in IOP from baseline to Week 1.

If no valid IOP is available at the Week 1, the last post-baseline before Week 1 will be utilized for imputation. If the prohibited treatment will be received, the IOP after prohibited treatment will not be utilized for imputation in PPS analysis. On the other hand, the IOP after prohibited treatment will be utilized in FAS analysis.

The change in IOP from baseline at Week 1 will be summarized descriptively. The point estimate and its two-sided 95% confidence interval using one-sample t-statistics will be calculated. The corresponding hypotheses for the efficacy analysis are

$$H_0: \mu \geq 0,$$
$$H_a: \mu < 0,$$

where μ is the change in IOP from baseline at Week 1. If the upper limit of the two-sided 95% confidence interval in PPS is less than the threshold (i.e., 0), the null hypothesis will be rejected and the study will be regarded as success.

Supplemental analysis

The same analysis will be conducted in the FAS. In addition, the same analysis of PPS will be conducted using observed case i.e., not apply imputation rule.

6.2.2 Secondary efficacy analysis

Secondary efficacy variable is

- Proportion of subjects who have improved NVI grade from baseline to Week 1.

Improvement by at least one grade from baseline will be categorized to “Improved”. The same imputation rule as IOP will be conducted.

The proportion of subjects who have improved NVI grade from baseline at Week 1 will be summarized descriptively. The point estimate and its two-sided 95% confidence interval using Clopper-Pearson method will be calculated. If the valid NVI is not available at Week 1

in spite of applying imputation rule, the subject will be regarded as not improve but included in denominator. The subject who do not have valid NVI at baseline will be excluded from this analysis, i.e. excluded from denominator even if the subject has valid/invalid NVI at Week 1.

Supplemental analysis

The same analysis will be conducted in the FAS. In addition, the same analysis of PPS will be conducted using observed case i.e., not apply imputation rule.

6.2.3 Exploratory efficacy analysis

Exploratory efficacy variables include, but not limited to, the followings:

- IOP and change from baseline to each visit,
- NVI and NVA and change from baseline to each visit, and
- Proportion of subjects who could control IOP (≤ 21 mmHg) at each visit.

Exploratory efficacy analyses will be conducted in the PPS. If FAS differs from the PPS, the same analyses will be also conducted in FAS.

6.2.3.1 IOP and change from baseline to each visit

The IOP and change from baseline to each visit will be summarized using summary statistics.

Graphical displays of individual data as well as mean values with SD will be included. Graphical displays of the change from baseline will be presented.

6.2.3.2 NVI and NVA and change from baseline to each visit

The same imputation rule as IOP (see Sec. 6.2.1) will be conducted. The change in NVI and NVA grades will be categorized to "Improved" (improvement by at least one grade from baseline), "Worsened" (worsened by at least one grade from baseline) or "Stable" (no change in grade from baseline).

The NVI and NVA grades and their change from baseline at each visit will be summarized descriptively using frequency tables. Graphical displays of the change from baseline will be presented.

In addition, for the proportion of subjects who have improved NVA grade from baseline at Week 1, the point estimates and its two-sided 95% confidence interval using Clopper-Pearson method will be calculated. If the valid NVI/NVA is not available at each visit even if the subjects continue the study, the subject will be regarded as "Missing" and included in the denominator. If the subjects discontinue the study before the visit, the subjects will not be included as denominator.

6.2.3.3 Proportion of subjects who could control IOP (≤ 21 mmHg) at each visit

The Proportion of subjects who could control IOP (≤ 21 mmHg) at each visit will be summarized descriptively using frequency tables. Graphical displays of the change from baseline will be presented.

In addition, for the Proportion of subjects who could control IOP (≤ 21 mmHg) at Week 1, the point estimates and its two-sided 95% confidence interval using Clopper-Pearson method will be calculated. If the valid IOP is not available at each visit even if the subjects continue the study, the subject will be regarded as "Missing" and included in the denominator. If the

subjects discontinue the study before the visit, the subjects will not be included as denominator.

6.2.3.4 Subgroup analyses

The subgroup analyses will be performed in primary variable and secondary efficacy variable. The subgroups will include:

- Age (years): < 65, ≥ 65;
- Sex: Male, Female;
- Primary Diagnosis: CRVO, PDR, OIS, other;
- IOP at Baseline group (mmHg): ≤ median, > median;
- NVI grade at baseline group: Grade 1 or 2, Grade 3 or 4;
- NVA grade at baseline group: Grade 1 or 2, Grade 3 or 4.

Graphical displays using forest plot will be included.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable.

6.4 Safety

The safety analyses will be conducted in the SAF.

6.4.1 Adverse events

AEs that occurred or worsened after the first dose of study drug and no later than 30 days after the last dose of study drug (i.e., not later than 30 days after the last injection) will be considered as treatment-emergent AE (TEAE).

Evaluations of AEs will be done for four sets of AEs, which will be identified from the information in the CRF:

- Ocular AE in the study eye,
- Ocular AE in the fellow eye,
- Non-ocular AE, and
- All AE (i.e., all AEs mentioned above combined).

Overall summary

Overall summary for AEs, pre-treatment AE, and TEAEs will be provided using frequency tables.

Incidence

The number of subjects with the following kinds of AE will be summarized using frequency tables presented by MedDRA Preferred Term (PT) within primary System Organ Class (SOC):

- Treatment-emergent AE,
- Treatment-emergent serious AE,
- Treatment-emergent study drug or intravitreal procedure-related AE,

- Treatment-emergent study drug-related AE,
- Treatment-emergent intravitreal procedure-related AE,
- Treatment-emergent protocol required procedures-related AE,
- Treatment-emergent serious study drug or intravitreal procedure-related AE,
- Treatment-emergent serious study drug-related AE,
- Treatment-emergent serious intravitreal procedure-related AE,
- Treatment-emergent serious protocol required procedures-related AE, and
- Treatment-emergent non-serious AE.

Incidence by Maximum intensity

The number of subjects with the following kinds of AE will be summarized using frequency tables presented by MedDRA PT within primary SOC by maximum intensity:

- Treatment-emergent AE and
- Treatment-emergent study drug-related AE.

Results of Antiplatelet Trialists' Collaboration (APTC) adjudication

An adjudication of AEs according to the APTC criteria will be performed. A frequency table of adjudication terms, cross-tabulated with related MedDRA PT terms, will be displayed.

Subgroup analysis

Treatment-emergent AEs and treatment-emergent study drug related AEs will be also summarized for the subgroups described in section 6.2.3.4.

The following subgroups will be considered only for safety evaluation.

- Renal impairment: Yes (CrCl ≤ 80 mL/min), No (CrCl > 80 mL/min) classified by creatinine clearance (CrCl) at baseline.
  CrCl is calculated according to the Cockcroft-Gault formula as below (Renal impairment guideline of FDA, 1998).

$$CrCl \approx \frac{[140 - age(years)] * weight(kg)}{72 * serum\ creatinine(mg/dl)} * \begin{cases} 1.0, if\ male \\ 0.85, if\ female \end{cases}$$

- Medical history of hepatic impairment: Yes, No
  - Subjects with the medical history of MedDRA PBMQ MedDRA SMQ "Hepatic disorders (SMQ)" (code=20000005) are considered "Yes"
- Medical history of hypertension: Yes, No
  - Subjects with the medical history of MedDRA PBMQ "Medical history of hypertension (VEGF Trap-Eye)" (code=SMQ_1275) are considered "Yes"
- Medical history of cerebrovascular accident (CVA) / Stroke: Yes, No
  - Subjects with one of the following medical history are considered "Yes"
    - MedDRA SMQ "Central nervous system vascular disorders (SMQ)" (code=20000060)

  - MedDRA SMQ "Central nervous system haemorrhages and cerebrovascular conditions (SMQ)" (code=20000061)
  - MedDRA SMQ "Ischaemic central nervous system vascular conditions (SMQ)" (code=20000063)
  - MedDRA SMQ "Haemorrhagic central nervous system vascular conditions (SMQ)" (code=20000064)

- Medical history of myocardial infarction (MI): Yes, No
  - Subjects with the medical history of MedDRA PBMQ "Medical history of myocardial infarction (VEGF Trap-Eye)" (code=SMQ_1278) are considered "Yes"

6.4.2 Listings of deaths, other serious and significant adverse events

Deaths, serious AEs will be listed by subject.

6.4.3 Pregnancies

The number of female subjects taking a pregnancy test will be summarized with the results.

6.4.4 Laboratory values

The absolute values and the change from baseline at each visit will be summarized for all quantitative parameters.

All laboratory values will be categorized according to the normal range:

- Laboratory results below the lower limit of the normal range will be "Low",
- Laboratory results within the normal range will be "Normal", and
- Laboratory results above the upper limit of the normal range will be "High".

The incidence of laboratory values outside normal range will be presented.

6.4.5 Vital signs

The absolute values and the change from baseline at each visit will be summarized for body temperature, blood pressure, and pulse rate.

6.4.6 Ophthalmic examinations

Unless otherwise specified, results for the study eye will be tabulated, and results for the fellow eye will be listed only.

Visual acuity

The number of subjects who meet the followings will be summarized, respectively using frequency tables:

- Visual acuity in decimal score was ≥ 0.01 at baseline but deteriorated to be not assessable or < 0.01 at post-baseline visit,
- Visual acuity in decimal score was > 0.1 at baseline but ≤ 0.1 at post-baseline visit, and
- Lost half of visual acuity in decimal score at post-baseline visit compared to baseline.

The absolute values and the change from baseline at each visit will be summarized using logMAR BCVA scores. The logMAR scores will be derived from the decimal scores as follows:

$$-1 \times \log_{10}(\text{Decimal score}).$$

For this purpose, BCVA categories lower to the minimum value assessable with the BCVA chart will be converted to decimal score as follows[2]:

Table 6-1 Conversion table for low visual acuity

Table Category	Visual acuity in decimal score
Count Fingers	0.005
Hand Motion	0.0025
Light Perception	0.00125
No Light Perception	0.0001

(Takihara Y et al, 2009)

Applanation tonometry

The absolute values and change from pre-dose IOP will be summarized for post-dose IOP.

Slit-lamp microscopy

A frequency table for each parameter of slit lamp microscopy, including lids, conjunctiva, cornea, anterior chamber, iris, pupil, lens, and other, will be displayed by visit. In addition, a separate frequency table for those subjects with 'abnormal' in any parameter measured will be given.

Frequency tables by visit will be provided for grading of anterior chamber flare and cells (categories: 0 / Trace / 1+ / 2+ / 3+ / 4+). Additionally, shift tables will be presented by visit.

Gonioscopy

A frequency table for gonioscopy will be displayed by visit. In addition, a separate frequency table for those subjects with 'abnormal' will be given.

Indirect ophthalmoscopy

A frequency table for each parameter of indirect ophthalmoscopy, including vitreous body, optic nerve head, macula, peripheral retina, and the number of quadrants affected by pathologic findings, will be displayed by visit. In addition, a separate frequency table for those subjects with 'abnormal' in any parameter measured will be given.

7. Document history and changes in the planned statistical analysis

Not applicable.

8. References

1. Hara T, Nakayama Shoten: Ophthalmologic diagnosis qualification for medical specialists 3 2011_1(1): p233

2. Takihara Y, Inatani M, Fukushima M, et al. Trabeculectomy with Mitomycin C for Neovascular Glaucoma: Prognostic Factors for Surgical Failure. American Journal of Ophthalmology. 2009; 147 (5): 912-8.